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Safety of Universal Provision of Iron through Home Fortification of Complementary Foods in Malaria-Endemic Areas[1,2]

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ABSTRACT

Home fortification of complementary foods with iron and other micronutrients is a low-cost strategy for filling nutrient gaps in the diets of infants and young children, but there has been uncertainty about the safety of universal provision of iron via home fortification in malaria-endemic areas. Based on the current understanding of the potential mechanisms of adverse effects of iron, the risk can probably be minimized by using the lowest possible efficacious dose of iron, preferably delivered in small amounts throughout the day with food, to minimize spikes in plasma nontransferrin-bound iron and large amounts of unabsorbed iron in the gastrointestinal tract. Results from 6 home fortification studies in malaria-endemic areas showed no increased risk of morbidity (including malaria), but these studies were not powered to rule out a modest increase in the risk of severe adverse events. At present, the safest option is to implement home fortification in the context of comprehensive malaria control strategies, as recommended in recent WHO guidelines. *Adv. Nutr. 3: 555–559, 2012.*

Introduction

In low-income populations, iron deficiency is generally very common during the period of complementary feeding, e.g., from 6 to 24 mo of age, as described in a companion paper (1). Much of this is attributable to very low intake of absorbable iron from complementary foods, relative to requirements. Thus, strategies to increase iron intake during this period are essential to avoid the deleterious effects of iron deficiency and iron-deficiency anemia on behavioral development and other outcomes. The question is whether it is better to take a targeted approach by providing iron only to those who have already become iron deficient, potentially avoiding deleterious effects of iron on those who are iron replete (2), or to provide iron to all children within a certain age range ("universal" or "blanket" provision) regardless of their iron status.

Although targeted provision of iron may be attractive from a biological perspective, there are several practical considerations that limit feasibility. Apart from the issue of finding an appropriate indicator of iron status that can be inexpensively and easily measured, the targeted approach requires that iron deficiency or anemia be detected via screening before iron is provided to a given child. Some children will therefore be iron deficient for quite some time before they receive additional iron, depending on the frequency of screening, which means that the critical window for preventing the adverse effects of iron deficiency may be missed. The targeted approach also complicates the situation with respect to addressing other micronutrient and macronutrient deficiencies during the period of complementary feeding because it would require that fortified products designed for universal use would *not* include iron, even though iron is usually the most limiting nutrient at this age.

In recent years, programmatic priorities have shifted toward taking a comprehensive approach to improving nutrition in infants and young children rather than focusing predominantly on programs that provide just 1 key nutrient at a time (e.g., iron supplementation). Improving complementary feeding involves a wide range of strategies to tackle the many dimensions of suboptimal feeding practices and dietary inadequacies (3). Within this spectrum, a number of options to improve iron content and bioavailability of

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complementary foods have been explored. Because these strategies are generally designed to prevent deficiency (rather to treat deficiency), they are mainly intended for universal implementation. Thus, it is important to evaluate the safety of universal provision of iron through such approaches, particularly in malaria-endemic areas. This paper focused on home fortification because this approach is currently being scaled up in several countries and is likely to be the most cost-effective strategy for improving nutrient density of complementary foods (4).

Biological plausibility for safety of home fortification with iron

Theoretical considerations regarding safety based on the amount of iron provided per meal. Iron content of complementary foods can be increased via several different strategies including a) dietary modification (e.g., increased intake of flesh foods and use of traditional food-processing techniques to enhance iron absorption from plant-based foods), b) iron-fortified processed complementary foods, and c) use of home fortification products [e.g., micronutrient powders (MNP)[3] or lipid-based nutrient supplements (LNS)]. Compared with the use of iron supplements (e.g., liquid iron drops), which are typically given between meals, the 3 strategies above all involve the provision of iron with food, which is known to slow iron absorption (5) and therefore modulate the potential physiological impact of the "bolus" of iron delivered.

Dietary modification strategies have generally had a relatively modest impact on iron status, mainly because the increase in iron content or bioavailability of complementary foods that is achievable by these means is limited (3). The safety of dietary modification strategies has not been questioned, however. Of the 2 strategies that involve fortification, commercially processed complementary foods can be fortified to provide the recommended nutrient intake (RNI) of iron (e.g., 9 mg/d at 7–12 mo of age, assuming 10% bioavailability (6)) in each daily ration, which is usually distributed across 2–3 meals per day. Each meal would thus provide 3–4.5 mg of iron if the full daily ration is consumed. In the statement emerging from the WHO technical consultation in 2006 (7), processed complementary foods fortified with iron were considered to be safe because they provide a physiological dose of iron distributed throughout the day, "which avoids the adverse gastrointestinal and morbidity effects of a bolus dose." However, the actual intake of iron from processed complementary foods may vary widely because of a large range in intake of the product across individuals (from as little as 10 g/d to as much as 100 g/d of the dry product). Efficacy with regard to improved iron status and reduced anemia may thus be less consistent than is achievable with strategies (such as home fortification) that can better ensure consumption of the intended dose of iron each day (3).

Iron content of home fortification products is typically ~1 RNI (e.g., 9–12.5 mg/d; the RNI varies depending on expected bioavailability of iron). If the entire daily dose is mixed with a single meal (as is usually the case with MNP), then the "bolus" of iron would be similar to that used in the iron supplementation trial in Pemba in which adverse effects were observed (8). For this reason, the statement emerging from the WHO technical consultation (7) advised that home fortification products "should not be used in malaria-endemic areas" (note that this statement has now been superseded by the recently published WHO guidelines on use of multiple micronutrient powders for home fortification (9) that state that such products can be used in malaria-endemic areas if "implemented in conjunction with measures to prevent, diagnose and treat malaria").

However, if the daily dose of the home fortification product is divided between ≥2 meals, then the amount of iron consumed per meal would be similar to that provided by processed fortified complementary foods. For example, if the daily ration of LNS used for home fortification includes 9 mg of iron and is divided between 2 meals, the iron consumed per meal would be 4.5 mg. Current research trials being conducted in Africa as part of the International Lipid-based Nutrient Supplements Project (10) are using LNS with a reduced amount of iron (6 mg/d), with participants being advised to divide the dose between 2 meals, thus delivering ~3 mg of iron per meal. Thus, home fortification can be designed to be as "safe" (theoretically) as processed fortified complementary foods. One advantage of the home fortification approach is that each child receives the intended amount of iron via the home fortification product, regardless of the amount of complementary food consumed.

Hypothesized mechanisms for the adverse effects of iron in malaria-endemic areas and implications regarding safety of home fortification. To evaluate whether home fortification with iron-containing products is likely to be safe in malaria-endemic areas, it is useful to consider the hypothesized mechanisms for the adverse effects of iron. At present, our understanding of these mechanisms is incomplete. Hurrell (5) describes 2 likely "candidate" pathways by which excess iron may be harmful. The first is that a large bolus of iron triggers a spike in plasma nontransferrin-bound iron (NTBI), which may induce cell damage via reactive oxygen radicals and increase inflammation. This may stimulate expression of endothelial adhesion molecules in capillaries and lead to increased sequestration of red bloods infected by the malaria parasite, impairing function of the microvasculature. NTBI entering the liver may also facilitate the penetration of hepatocytes by malaria sporozoites. The second hypothesized pathway is that iron stimulates growth of enteric pathogenic organisms, which may impair the innate immune response of the gastrointestinal tract and lead to bacterial invasion through the gut into the systemic circulation, causing bacteremia and septicemia. Iron may influence morbidity and mortality by either, both, or perhaps neither of these routes.

The first of these 2 hypothetical pathways is illustrated in **Figure 1**. Because the rate of iron influx into plasma exceeds the rate at which iron binds to transferrin, iron can appear as

[3] Abbreviations used: LNS, lipid-based nutrient supplement; MNP, micronutrient powder; NTBI, nontransferrin-bound iron; RNI, recommended nutrient intake.

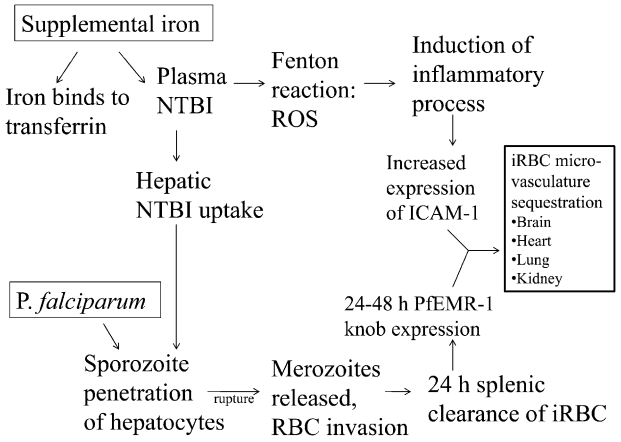

Figure 1 Postulated effect of NTBI on severity of malaria. ICAM-1, intercellular adhesion molecule; iRBC, infected red blood cell; NTBI, nontransferrin-bound iron; PfEMR-1, *Plasmodium falciparum* erythrocyte membrane protein 1; ROS, reactive oxygen species. Adapted from Reference 5 with permission.

NTBI in the plasma. NTBI is thought to contribute to iron toxicity due to its role in the Haber-Weiss and Fenton reactions that generate reactive oxygen species. Reactive oxygen species induce cell damage through the oxidation of lipids, proteins, and DNA.

Malaria may exacerbate the damage due to NTBI. Iron is absorbed through the gut and enters the hepatic portal system. Thus, the concentration of NTBI reaching the liver is expected to be far higher than the concentration detected in plasma. Immature forms of the malaria parasite, sporozoites, are introduced into the circulation by the mosquito vector and occupy the liver. An increased supply of iron in the liver may facilitate penetration of hepatocytes by sporozoites, leading to the development of merozoites, the form of malaria parasite that infects red blood cells.

In severe cases of malaria, parasitized red blood cells adhere to adhesion molecules expressed on the surface of endothelial cells lining blood vessels. Up-regulation of adhesion molecules on the endothelia of the microvasculature occurs in response to proinflammatory mediators during an episode of malaria. After 24–48 h in the circulation, parasitized red blood cells begin to express "knobs" capable of binding adhesion molecules and are sequestered from circulation. Sequestration of infected red blood cells prevents removal by the spleen and occludes the microvasculature, leading to the symptoms of severe malaria. Therefore, if excess iron increases the number of merozoites and infected red blood cells, this would increase the risk of damage to the microvasculature.

The magnitude of the effects illustrated in Figure 1 is likely to be related to the amount of NTBI entering the plasma, which depends on the amount of iron absorbed after ingestion. The total amount of iron absorbed will be lower under certain conditions, such as when a) the dose of iron is relatively low; b) iron is consumed with food, which reduces absorption by as much as two thirds (5); c) the individual is iron replete; and d) there is clinical or subclinical infection or inflammation, which reduces iron absorption. Because home fortification can be designed to provide relatively small amounts of iron per meal and the iron is always ingested with food, it should be possible to minimize the effects illustrated in Figure 1.

However, strategies that prevent large spikes in absorbed iron may not be sufficient to eliminate all of the risks associated with excess dietary iron. As illustrated in **Figure 2**, the *unabsorbed* iron remaining in the gastrointestinal tract may foster the growth of less beneficial, even pathogenic, bacteria in the colon. Iron acquisition is essential for the growth of enteric pathogenic organisms such as *Salmonella*, *Shigella*, and pathogenic *Escherichia coli*, whereas beneficial gut bacteria such as lactobacilli and bifidobacteria do not require an external source of iron. Thus, unabsorbed iron may mediate the growth of enteric pathogenic bacteria and impede the competitive inhibition of pathogenic strains by beneficial strains. Evidence supporting this phenomenon is provided by a recent randomized, controlled trial among school-age children in Côte d'Ivoire in which iron-fortified biscuits provided for 6 mo resulted in a more unfavorable ratio of fecal enterobacteria to bifidobacteria and lactobacilli and an increase in a marker of gut inflammation (11). Gastrointestinal tissue damage may be a gateway for pathogenic organisms to enter the circulation. In combination with malaria, which may itself alter gut permeability because intestinal villi are favored sites of sequestration for parasitized red blood cells, excess iron in the gut could increase the risk of bacteremia. This is supported by the fact that one of the complications of severe malaria is non-typhi *Salmonella* bacteremia (12).

These 2 hypothesized pathways—spikes in NTBI and increased growth of enteric pathogens—may jointly contribute to the adverse effects of iron in malaria-endemic areas, as illustrated in **Figure 3**. It is noteworthy that the adverse effects observed in the Pemba trial were related to the *severity* of malaria (i.e., hospitalization) and overall mortality, not necessarily an increase in the *incidence* of malaria, which is consistent with the endpoints shown in Figure 3.

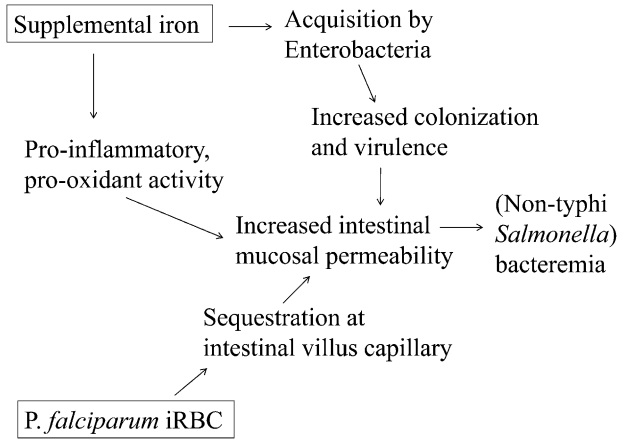

Figure 2 Postulated effect of supplemental iron on bacteremia. iRBC, infected red blood cell. Adapted from Reference 5 with permission.

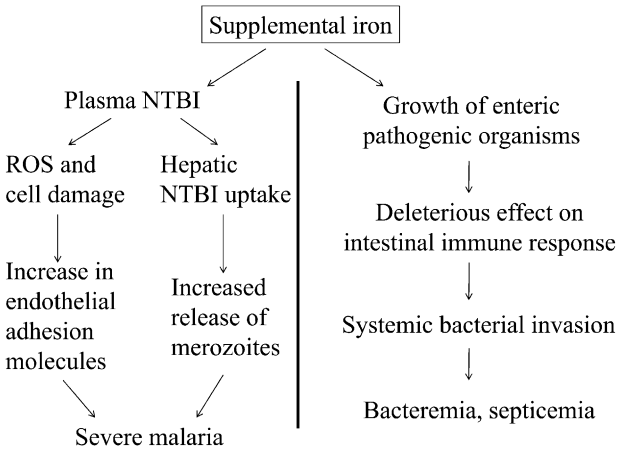

Figure 3 Pathways that may jointly contribute to adverse effects of supplemental iron in malaria-endemic areas. NTBI, nontransferrin-bound iron; ROS, reactive oxygen species. Adapted from Reference 5 with permission.

As mentioned previously, our understanding of the mechanisms underlying the adverse effects of excess iron is still very incomplete. If, however, the pathways shown in Figure 3 are at least part of the picture, the implication is that interventions to improve the iron status of young children should aim at the lowest possible efficacious dose of iron, preferably delivered in small amounts throughout the day with food, to minimize spikes in NTBI and large amounts of unabsorbed iron in the gastrointestinal tract.

Evidence regarding safety of home fortification with iron

Empirical evidence regarding the safety of home fortification of complementary foods in malaria-endemic areas is very limited. We were able to identify only 6 relevant studies (13–17), 3 of which have not yet been fully published. Details of the 3 published randomized, controlled trials were described in a previous review on home fortification (4). These include a trial using crushable micronutrient tablets in South Africa (13), MNP in Pakistan (14), and 3 different types of home fortification products (MNP, crushable tablets, and LNS) in Ghana (15). Malaria was not a primary outcome in any of these studies, but the percentage of days with fever (often caused by malaria) was assessed in South Africa and Ghana. In South Africa (N = 265), there were no significant differences in the percentage of children with fever on the day of contact with the health worker (during weekly morbidity surveillance over the 6-mo intervention period) among the 4 intervention groups: placebo, 13.4%; daily iron (10 mg/d), 10.1%; daily multiple micronutrients, 10.6%; and weekly multiple micronutrients (containing 20 mg of iron per week), 12.2%. Similarly, in Ghana (N = 409), there were no significant differences among any of the 3 intervention groups (who received 9–12.5 mg iron/d) and the nonintervention group in the percentage of children with fever during the 1-wk period before the end of the 6-mo intervention period or in the mean percentage of days with fever during the intervention among the 3 intervention groups (3.3% for MNP, 5.3% for crushable tablets, and 4.3% for LNS). These 2 studies also showed no significant differences in prevalence of diarrhea among the 3 intervention groups. The trial in Pakistan, conducted with 75 infants with a history of diarrhea, showed a significant reduction in longitudinal prevalence of diarrhea in the MNP group (15%) compared with the placebo group (26%) (P = 0.009) after 2 months of supplementation.

In the 3 other trials (in Kenya, Ghana, and Malawi), malaria incidence was documented. In western Kenya, a cluster-randomized trial was conducted to assess the impact of community-based marketing of MNP (Sprinkles, Ped-Med, Ltd., Toronto, Canada) (16). Sixty villages were randomly assigned to the intervention or control group; in the intervention villages, community vendors sold Sprinkles targeted at children between 6 and 59 mo of age. The baseline survey was conducted in July 2007, the intervention was implemented 3 mo later, and the follow-up survey (N = 862) was conducted in March 2008; after that, the project package was implemented in the control villages. The surveys included children 6–35 mo of age. During biweekly household visits in the intervention villages, 33% of households had purchased Sprinkles in the previous 2 wk; average weekly intake was 0.9 sachets/wk, contributing ~11 mg of iron per week. Despite this relatively small increase in iron intake, there were significant differences in the prevalence of iron deficiency and in mean hemoglobin values between intervention and control villages. There was no significant difference in the rate of malaria parasitemia between groups.

In Ghana, a randomized, controlled trial was conducted to determine the impact of providing iron in MNP on the incidence and severity of malaria in an area with a high burden of malaria (17). In total, 1956 children 6–35 mo of age were randomized to receive MNP (Sprinkles) daily for 5 mo; 1 group received MNP with the usual amount (12.5 mg) of iron (as ferrous fumarate), and the other group received MNP with no iron. Malaria status was assessed at weekly home visits. There were no significant differences between groups in the incidence of malaria or severe adverse outcomes such as cerebral malaria and hospitalizations.

The intervention in Malawi was of longer duration (12 mo) than the intervention period in the 2 trials described above (5–6 mo) and involved the delivery of iron via LNS rather than MNP. The Lungwena Child Nutrition Intervention-5 study was a randomized intervention trial in which infants (N = 840) were randomly assigned at 6 mo of age to 1 of 4 intervention groups: a) LNS (the usual formulation that includes milk powder), b) LNS with soy in place of milk powder, c) fortified maize-soy flour (isocaloric daily dose), or d) control (delayed intervention). Iron content of the products was 6 mg/d in LNS and 5.5 mg/d in the maize-soy flour. Morbidity surveillance was conducted weekly. There were no significant differences among groups in the percentage of children with confirmed malaria during the 12-mo intervention period (excluding cases of malaria at enrollment) or in the mean percentage of days with fever, cough, or diarrhea (K. Maleta, personal communication).

The lack of adverse effects in the cited trials is somewhat reassuring, but for several reasons, it is difficult to draw definitive conclusions about safety. First, some of the interventions were of relatively short duration (<6 mo), which limits the ability to detect effects that may be cumulative or not apparent until the average iron status reaches a certain threshold. Second, the dose of iron in some of the trials was modest (especially the marketing trial in Kenya), so generalizations regarding the safety of higher doses may not be warranted. Third, none of the studies have so far reported on whether initial iron status has an influence on treatment effects. Given that the Pemba trial found that children with higher iron status were more vulnerable to adverse effects of iron supplementation [in the subsample analyses (8)], it is important to conduct subgroup analyses if sample size permits. Last, even the largest of these trials, the study in Ghana with almost 2000 children, is still not sufficiently powered to detect relatively small effects on adverse outcomes such as were seen in the Pemba trial.

Conclusions

Home fortification of complementary foods is gaining visibility as an effective approach for increasing intake of iron and other micronutrients by infants and young children at risk of nutrient deficiencies. It is probably a safer option than iron supplements given without food, although evidence directly comparing the safety of these 2 approaches in malaria-endemic areas is lacking. Results from 6 home fortification studies in malaria-endemic areas (some not yet published) showed no increased risk of adverse effects. Most of these studies, however, had small to moderate sample sizes, so severe adverse events could not be adequately assessed. There is also a lack of information on the potential modifying effect of initial iron status on treatment effects. Although the evidence to date suggests that home fortification with iron in malaria-endemic areas is safe, additional research would be valuable.

However, it is very challenging, if not impossible, to obtain conclusive evidence of the safety of home fortification in malaria-endemic areas. Severe adverse events associated with iron consumption are likely only seen where infectious disease control is lacking, yet it would be unethical in this type of setting to conduct studies without providing any services to monitor and treat infectious disease, including malaria. A huge sample size would be required to rule out a modest increase in severe adverse effects. For the moment, the safest option is to deliver home fortificants in the context of comprehensive malaria control strategies, as recommended in the recent WHO guidelines on the use of MNPs (9). The evidence to date indicates that universal provision of iron is safe in populations with adequate malaria surveillance and treatment (18). As home fortification programs are rolled out, it would be highly desirable to structure program implementation to facilitate rigorous evaluation of the effectiveness and safety of such interventions. This may help to answer the remaining question of how to safely ensure adequate iron status of infants and young children in populations *without* adequate malaria surveillance and treatment.

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